Remarks

Claims 17-18, 22-24, and 44-72 were pending in the subject application. Claims 17-18 and 22-24 have been withdrawn from consideration by the Examiner as drawn to nonelected subject matter. By this amendment, applicants have canceled claims 17-18 and 22-24 with prejudice or disclaimer. Accordingly, after entry of this amendment, claims 44-72 will be pending and under consideration.

Objection under 37 C.F.R. § 1.126

On page 2 of the August 28, 2002 Final Office Action, the Examiner objected to previously filed claims 30-58 as being misnumbered under 37 C.F.R. §1.126. The Examiner stated that 37 C.F.R. §1.126 requires that the original numbering of the claims be preserved throughout the prosecution. Accordingly, the Examiner renumbered misnumbered claims 30-58 as claims 44-72.

Applicants attach hereto a clean copy of renumbered pending claims 44-72.

Accordingly, applicants respectfully request withdrawal of the objection under 37 C.F.R. §1.126.

Rejection under 35 U.S.C. §112, first paragraph

On page 3 of the Final Office Action, the Examiner rejected claim 48 under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. The Examiner stated that applicants fail to point out where in the specification there is support for the phrase "comprising 12 transmembrane domains as determined by hydropathy plot analysis" .

In response, applicants respectfully point out that support for the claim recitation "comprising 12 transmembrane domains as determined by hydropathy plot analysis" is

found at page 40, lines 1-3 of the specification as originally filed.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph

On page 3 of the Final Office Action, the Examiner rejected claims 44-72 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph as allegedly lacking utility and enablement. The Examiner asserted that the specification fails to establish that the disclosed polynucleotide sequences encode a protein which is a member of the glucose transporter/sensor/receptor family. Applicants respectfully request reconsideration and withdrawal of these rejections in light of the following discussion.

The Examiner asserts that the instant invention is not considered to have a specific and/or substantial utility because the specification fails to establish that the polynucleotide sequences as claimed encode a protein which is a member of the glucose transporter/sensor/receptor family as shown by structural and/or functional properties. However, applicants contend that the specification provides sufficient evidence to establish to the skilled artisan that the disclosed nucleotide sequences (SEQ ID NOs 6, 9 and 11) are portions of sequences encoding human, mouse and rat versions, respectively, of a novel member of the GLUT family (designated GLUTx).

"An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g. properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible" (MPEP 2107 (A) (3)). "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g. printed publications) that is

probative of the applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement" (MPEP 2107 (B) (1) (ii)).

Applicants note that GLUTx comprises 12 transmembrane domains, which is characteristic of the GLUT family of glucose transporter (see specification, page 40, lines 1-3, and Ibberson et al. JBC, 275 (7): 4607-4612, 2000, page 4607, right column, first full paragraph). Furthermore, on page 29, lines 3-11, the specification discloses that:

> GLUTx has significant homology to facilitative glucose transporters such as GLUT4 and GLUT1 and has conserved amino acids known to be important in glucose binding. Additionally, GLUTx contains amino acid motifs present only in the glucose sensor/receptors SNF3 and RGT2, and has been detected using in situ hybridization techniques in the cerebellum and hippocampus of GLUT4 null mice, areas corresponding to the "obesity center" of the human brain. These findings suggest that GLUTx functions as a glucose sensor/receptor that assists in maintenance of normal blood glucose and possibly, the control of appetite and regulation of obesity.

In addition, on page 34, lines 1-8, the specification discloses:

> Partial sequence of GLUTx corresponding to the area between the 10th transmembrane domain and the carboxy-terminus of known mammalian GLUTs is shown in Figure 6. This area includes tryptophans 387 and 412 which are known to be important in glucose sensing and transport (Schurmann, et al., *Biochem J* 290: 497-501, 1993) and a highly conserved area in all transporters just outside the 12th transmembrane domain (PETxG). Approximately 45% sequence similarity is noted between GLUT4 and GLUTx in the region shown in Figure 6.

The homology values reported in the subject application are consistent with reports in the literature for the GLUT glucose transporters. For example, Ibberson et al. report that "[s]equence comparison indicated that rat GLUTX1 was 29-32% identical to

the GLUTs, whereas the GLUTs are between 40 and 70% identical to each other." (Ibberson et al. JBC, 275 (7): 4607-4612, 2000; see page 4611, right column, first full paragraph.) In addition, Doege et al. reported that the amino acid sequence of GLUT8 is 29.4% identical to that of GLUT1(Doege et al. JBC, 275 (21): 16275-16280, 2000, see Abstract). Both Ibbertson et al. and Doege et al. were previously cited by the Examiner. Furthermore, according to Olson and Pessin, "Only 38% of all the amino acids are conserved between the GLUT1- 4 isoforms..." (Olson and Pessin, Annu. Rev. Nutr. 16: 235-236, 1996, page 240, provided in the Information Disclosure Statement of June 25, 2002).

With further regard to the utility and enablement of the invention, applicants note that the present invention provides nucleic acid probes, which may be DNA or RNA varying in length from about 8 nucleotides to the entire length of the GLUTx nucleic acid, and mixtures thereof which are hybridizable to the nucleic acid encoding GLUTx (see, Specification, page 15, lines 6-7 and line 17). The nucleic acid probes may be labeled using one of a number of methods known in the art, e.g., PCR, nick translation, end labeling, fill-in end labeling, polynucleotide kinase exchange reaction, random priming, or SP6 polymerase (for riboprobe preparation) and one of a variety of labels, e.g., radioactive labels such as ^{35}S, ^{32}P or ^{3}H or nonradioactive labels such as biotin, fluorescein (FITC), acridine, cholesterol or carboxy-X-rhodamine (ROX). Combinations of two or more nucleic probes corresponding to different or overlapping regions of the GLUTx nucleic acid may also be included in kits for use in a variety of detection and diagnostic applications. See, page 15, lines 18-26.

Further, the present invention also provides methods for detecting increased or decreased expression of GLUTx by nucleic acid hybridization and/or immunological

techniques well known in the art (see, Specification, page 16, lines 1-3). Nucleic acid hybridization using mRNA extracted from cells and GLUTx nucleic acid probes can be used to determine the concentration of GLUTx mRNA present in the cell, which in turn can be compared to the value obtained for cells which exhibit a normal level of GLUTx activity (see, Specification, page 16, lines 3-7).

Further, the specification discloses that the livers and placentas of diabetic and hyperglycemic animals show a 2 to 3 fold upregulation of GLUTx mRNA compared to normal animals (page 39, lines 23-25). Thus, GLUTx has specific, credible, and substantial utility as a marker of diabetes and hyperglycemia, independently of GLUTx functioning as a glucose transporter.

The Examiner also asserted that the instant specification fails to provide any guidance that a nucleotide sequence that hybridizes under stringent hybridization conditions to a nucleotide sequence selected from SEQ ID NOs: 6, 9 and 11 has any GLUT1, GLUT2, GLUT3, GLUT4 or GLUT5 like activity.

In response, applicants further point out that using the methods outlined in the specification (page 33, line 24 through page 35, line 4), the inventors obtained the partial nucleotide sequences (together with the deduced amino acid sequences) encoding for human, rat and mouse GLUTx. Applicants assert that amino acid sequences of the GLUT isoforms has revealed a similar size between these proteins with the same overall topology yet "[d]espite this overall similar structural organization, there is considerable divergence in the specific amino acid sequences. Only 38% of all the amino acids are conserved between the GLUT1- 4 isoforms, and in general, the greatest degree of amino acid sequence identity lies within the transmembrane domains, with the most divergence in the large hydrophilic domain and in the amino and carboxyl termini..." (Olson and

Pessin, Annu. Rev. Nutr. 16: 235-236, 1996, page 240, provided in the Information Disclosure Statement of June 25, 2002 and incorporated by reference in its entirety into the subject application (see page 33, line 28-29, and page 40, lines 9-10 of the specification)). This is consistent with the sequence characteristics of GLUT8, a novel member of the sugar transport facilitator family with glucose transport activity. See, Doege, et al., 2000, J. Biol. Chem. 275:16275-16280, provided with the March 1, 2002 Office Action. Within the coding region of mouse and human GLUT8, 85.2% of the nucleotides and 86.2% of the amino acids are identical yet the deduced amino acid sequence of human GLUT8 is only 29.4% identical with that of GLUT1. See, Doege, et al., 2000, J. Biol. Chem. 275:16275-16280, provided with the March 1, 2002 Office Action. Applicants also note that the homology values of the instant invention are consistent with values that would be expected between various members of the GLUT family. See, e.g., Ibberson et al., 2000, J. Biol. Chem. 275:4607-4612, provided with the March 1, 2002 Office Action, where the abstract notes that the GLUTX1 glucose transporter has between 29 and 32% identity with rat GLUT1-5 and 32-36% identity with plant and bacterial hexose transporters. In light of the specification, Ibberson et al., Olson and Pessin, and Doege et al., the skilled artisan would understand that the identities provided in the instant specification for GLUTx would be expected for a novel glucose transporter. Those identity values thus would provide evidence to a skilled artisan that the disclosed sequences are indeed for a novel glucose transporter.

Based on the above discussion, applicants assert that the claimed invention fulfills the requirement of 35 U.S.C. §101 as having a "specific, substantial, and credible use ... set forth for the invention". (MPEP 2164.07). Further, applicants maintain that the claimed invention fulfills the requirements of 35 U.S.C. §112, first paragraph, in that since the claimed invention is supported by a credible asserted utility, the skilled artisan

would know how to use the claimed invention.

Rejection 35 U.S.C. §112, first paragraph

On page 7 of the Final Office Action, the Examiner rejected claims 44-72 under 35 U.S.C. §112, first paragraph, for allegedly failing to meet the written description requirement of 35 U.S.C. §112, first paragraph.

The Examiner asserted that the instant specification discloses only a single species which is not representative of the variants of the genus and thus fails to describe the features of the genus. Applicants respectfully request reconsideration and withdrawal of this rejection in light of the following discussion.

Applicants assert that the pending claims are directed to sequences described in the specification that bind under high stringency to the exemplified sequences. SEQ ID Nos. 6, 9, and 11 are described in the Sequence Listing and in Figures 9, 11, and 13, respectively. SEQ ID Nos. 7, 10, and 12 are described in the Sequence Listing and in Figures 10, 12, and 14, respectively. High stringency conditions are described in the specification on page 8, lines 27-29. Accordingly, applicants respectfully maintain that the claimed invention is described in the specification in sufficient detail that one skilled in the art would reasonably conclude that the inventors had possession of the claimed invention.

Conclusion

In light of the claim amendments and the above remarks, applicants respectfully request withdrawal of all objections and rejections and passage of the currently pending claims 44-72 to allowance. If there are any minor matters that would prevent allowance of the claims, applicants request that the Examiner contact the undersigned attorney.

No fee is deemed to be required to maintain the pendency of this application.

However, if there are unanticipated fees required to maintain the pendency of this application, the PTO is authorized to withdraw those fees from Deposit Account 01-1785. Overcharges may also be credited to Deposit Account 01-1785.

Respectfully submitted,

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Currently Pending Claims - 09/516,493

44. An isolated nucleic acid sequence, the sequence comprising at least 1362 nucleotides, that hybridizes under high stringency conditions to a nucleotide sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:9, SEQ ID NO:11, the complement of SEQ ID NO:6, the complement of SEQ ID NO:9, and the complement of SEQ ID NO:11.

45. The isolated nucleic acid sequence of claim 44, wherein the sequence hybridizes under high stringency conditions to SEQ ID NO:6 or the complement of SEQ ID NO:6.

46. The isolated nucleic acid sequence of claim 44, wherein the sequence hybridizes under high stringency conditions to SEQ ID NO:9 or the complement of SEQ ID NO:9.

47. The isolated nucleic acid sequence of claim 44, wherein the sequence hybridizes under high stringency conditions to SEQ ID NO:11 or the complement of SEQ ID NO:11.

48. The isolated nucleic acid sequence of claim 44, wherein the nucleic acid sequence or its complement encodes an amino acid sequence comprising 12 transmembrane domains, as determined by hydropathy plot analysis.

49. The isolated nucleic acid sequence of claim 44, wherein the sequence is identical or complementary to at least a portion of SEQ ID NO:6.

50. The isolated nucleic acid sequence of claim 44, wherein the sequence is identical or complementary to at least a portion of SEQ ID NO:9.

51. The isolated nucleic acid sequence of claim 44, wherein the sequence is identical or complementary to at least a portion of SEQ ID NO:11.

52. The isolated nucleic acid sequence of claim 44, wherein the sequence is identical or complementary to SEQ ID NO:6.

53. The isolated nucleic acid sequence of claim 49, wherein the sequence comprises nucleotides 11 to 1372 of SEQ ID NO:6.

54. The isolated nucleic acid sequence of claim 52, comprising SEQ ID NO:6.

55. The isolated nucleic acid sequence of claim 44, wherein the nucleic acid sequence encodes SEQ ID NO:7.

56. The isolated nucleic acid sequence of claim 44, wherein the nucleic acid sequence encodes SEQ ID NO:10.

57. The isolated nucleic acid sequence of claim 44, wherein the nucleic acid sequence encodes SEQ ID NO:12.

58. The isolated nucleic acid sequence of claim 55, wherein the amino acid sequence is SEQ ID NO:7.

59. The isolated nucleic acid sequence of claim 44, wherein expression of the sequence is increased in a mammal in response to hyperglycemia or insulinopenia.

60. The isolated nucleic acid sequence of claim 44, wherein the nucleic acid sequence is RNA.

61. The isolated nucleic acid sequence of claim 60, wherein the RNA is mRNA.

62. The isolated nucleic acid sequence of claim 44, wherein the nucleic acid sequence is DNA.

63. The isolated nucleic acid sequence of claim 62, wherein the nucleic acid sequence is cDNA.

64. A probe comprising the nucleic acid sequence of claim 44, wherein the nucleic acid sequence is labeled.

65. The probe of claim 64, wherein the nucleic acid sequence is labeled with a radioactive label.

66. A vector comprising the nucleic acid sequence of claim 62.

67. A host cell transformed by the vector of claim 66.

68. The host cell of claim 67, wherein the host cell is a prokaryotic cell.

69. The host cell of claim 67, wherein the host cell is a eukaryotic cell.

70. A method for producing the nucleic acid sequence of claim 62, the method comprising growing a host cell, the host cell comprising a vector comprising the nucleic acid sequence of claim 62, and isolating the nucleic acid sequence from said culture.

71. The method of claim 70, wherein the host cell is a prokaryotic cell.

72. The method of claim 70, wherein the host cell is a eukaryotic cell.